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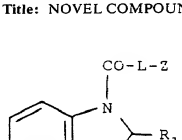
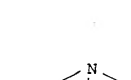


(I)



(a)

(b)

(c)

(57) Abstract

Compounds of formula (I), and pharmaceutically acceptable salts thereof, wherein L is NH or O; either R_1 is methyl, R_2 is hydrogen and R_3 is hydrogen; R_1 is methyl, R_2 is methyl and R_3 is hydrogen; or R_1, R_2 and R_3 are all methyl; or R_1 is hydrogen, R_2 is isopropyl and R_3 is hydrogen; or R_1 is hydrogen and R_2 and R_3 together are $-(CH_2)_4-$; Z is a group of formulae (a), (b) or (c), wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R_4 or R_5 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl; having 5-HT_3 receptor antagonist activity, a process and intermediates for their preparation and their use as pharmaceuticals.

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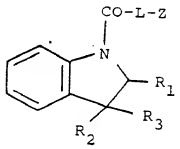
NOVEL COMPOUNDS

This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

EP-A-247266 (Beecham Group p.l.c.) describes a group of compounds possessing 5-HT_3 receptor antagonist activity.

A group of novel compounds, hitherto not specifically disclosed, has now been discovered. These compounds also have 5-HT_3 receptor antagonist activity.

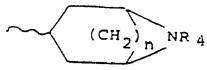
Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



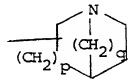
(I)

wherein
L is NH or O;
either
R_1 is methyl, R_2 is hydrogen and R_3 is hydrogen; or
R_1 is methyl, R_2 is methyl and R_3 is hydrogen; or
R_1, R_2 and R_3 are all methyl; or
R_1 is hydrogen, R_2 is isopropyl and R_3 is hydrogen; or
R_1 is hydrogen and R_2 and R_3 together are $-(CH_2)_4-$;

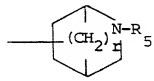
Z is a group of formula (a), (b) or (c)



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_4 or R_5 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl.

Preferably L is NH.

Preferably n is 2 or 3 and p, q and r are 1 or 2.

Examples of R_4/R_5 when C_{1-7} alkyl include as groups of interest C_{1-3} alkyl such as methyl, ethyl and n- and iso-propyl. Within C_{1-7} alkyl, C_{4-7} alkyl are also of interest, especially those of the formula $(CH_2)_uR_9$ wherein u is 1 or 2 and R_9 is a secondary or tertiary C_{3-6} alkyl group. Examples of C_{4-7} alkyl include n-, sec- and tert-butyl, n-pentyl, n-heptyl, and iso-butyl,

3-methylbutyl, and tert-butylmethyl.

Examples of R_4/R_5 when C_{3-8} cycloalkyl-C_{1-2} alkyl include in particular those wherein the cycloalkyl moiety is cyclohexyl or cyclopropyl. Examples include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, tert-butylmethyl, iso-propylmethyl, iso-propylethyl and tert-butylethyl.

R_4/R_5 may in particular be cyclopropylmethyl, cyclohexylmethyl, iso-propylmethyl, tert-butylmethyl or iso-propylethyl, preferably tert-butylmethyl.

Examples of R_4/R_5 when C_{2-7} alkenyl-C_{1-4} alkyl include prop-2-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl and 1-methyl-prop-2-enyl in their E and Z forms when stereoisomerism exists.

R_4/R_5 is preferably methyl or ethyl, most preferably methyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, lactic, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric,

sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_{10}-T wherein R_{10} is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

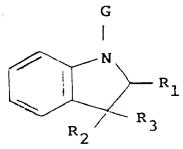
The compounds of formula (I) may also form internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that compounds of formula (I) may adopt an endo or exo configuration with respect to L. The endo configuration is preferred.

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

$$J\text{-}Z^1 \qquad \text{(III)}$$

wherein
G is COQ_1, where Q_1 is a leaving group, or hydrogen; and, when G is COQ_1, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula (II); Z^1 is Z as defined or Z wherein R_4/R_5 is replaced by a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo; C_{1-4} alkoxy, such as CH_3O and C_2H_5O-; PhO-;

activated hydrocarbyloxy, such as Cl_5C_6O- or Cl_3CO-; succinimidyloxy; and imidazolyloxy. Preferably Q_1 is halogen, most preferably chloro.

If a group Q_1 is a halide or imidazolyloxy, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0-100°C, in particular 10-80°C are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy, activated hydrocarbyloxy or succinimidyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene or dimethylformamide. In this instance, it is preferred that the group Q_1 is Cl_3CO- or succinimidyloxy and that the reaction is carried out in toluene at reflux temperature.

When J is OH or a reactive derivative thereof, the reactive derivative is often a salt, such as the lithium, sodium or potassium salt.

When G is hydrogen, J-Z^1 may be a compound of formula (IV) or (V) when L is NH; or of formula (VI) when L is O:

$$O=C=N-Z^1 \qquad (IV)$$

$$Q_2-\overset{O}{\overset{\|}{C}}-NH-Z^1 \qquad (V)$$

$$Q_3-\overset{O}{\overset{\|}{C}}-O-Z^1 \qquad (VI)$$

wherein
Z^1 is as hereinbefore defined, and Q_2 and Q_3 are leaving groups, preferably Cl_3CO and Cl respectively.

When $J-Z^1$ is of formula (IV), the reaction is preferably carried out in an inert solvent, under conventional conditions 0-100°C.

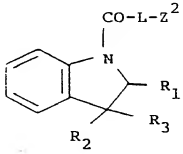
Q_2 is a leaving group as defined for Q_1 hereinbefore; and the reaction is carried out in accordance with the conditions described herein for the reaction wherein G is COQ_1.

Examples of Q_3, displaceable by a nucleophile, include halogen, such as chloro and bromo; and activated hydrocarbyloxy, such as Cl_5C_6O- and Cl_3CO.

If a group Q_3 is a halide, the reaction is carried out as described above for Q_1 halide.

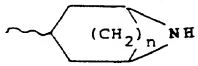
If Q_3 is activated hydrocarbyloxy, the reaction is carried out as described for Q_1 activated hydrocarbyloxy.

Z^1 when other than Z may have a hydrogenolysable protecting group which is optionally substituted benzyl. Such benzyl groups may be removed by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (VII):

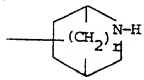


(VII)

wherein Z^2 is of formula (d) or (e):



(d)



(e)

wherein the variables are as defined in formula (I).

This invention also provides a further process for the preparation of a compound of the formula (I) which comprises N-alkylating a compound of formula (VII), and optionally forming a pharmaceutically acceptable salt, of the resulting compound of the formula (I).

In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (VII) by any group R_4/R_5 as hereinbefore defined. This may be achieved by reaction of the compound of formula (VII) with a compound R_4Q_4 or R_5Q_4 wherein R_4 and R_5 are as hereinbefore defined and Q_4 is a leaving group.

Suitable values for Q_4 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$.

Favoured values for Q_4 include Cl, Br and I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slight above.

Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions when the group R_4 or R_5 in the compound of formula (I) contains a methylene group adjacent to the N-atom in the bicycle.

Interconverting R_4 or R_5 in the compound of the formula (VII) before coupling with the compound of the formula (II) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R_4/R_5 interconversion.

When R_4 or R_5 in the compound of formula (III) contains a methylene group adjacent to the N-atom in the bicycle it is often convenient in the preparation of such a compound of formula (III) to prepare the corresponding compound wherein the methylene group is replaced by -CO-, or for R_4 or R_5 is methyl, where the methyl group is replaced by esterified carboxyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (II).

The compounds of formula (II) and (III) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of the formula (VII) are novel and form an aspect of the invention.

It will be realised that in the compound of the formula (I) the -CO-L-linkage may have an endo or exo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo and exo isomer may if desired be synthesised from the corresponding endo or exo form of the compound of the formula (III).

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally. The acid addition salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT_3 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of emesis, migraine, cluster headaches, trigeminal neuralgia and visceral pain. Compounds which are 5-HT_3 antagonists may also be of potential use in the treatment of CNS disorders such as anxiety and psychosis; drug withdrawal syndrome; arrhythmia, obesity and irritable bowel syndrome.

Anti-emetic activity includes that of preventing cytotoxic agent or radiation induced nausea and vomiting. Examples of cytotoxic agents include cisplatin, doxorubicin and cyclophosphamide.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of migraine, cluster headache, trigeminal neuralgia, visceral pain and/or emesis in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

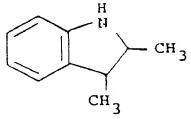
No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of migraine, cluster headache, trigeminal neuralgia, visceral pain and/or emesis.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions illustrate the preparation of intermediates.

Description 1

2,3-Dihydro-2,3-dimethylindole (D1)



(D1)

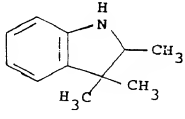
Following the procedure outlined by G.W. Gribble and J.H. Hoffman, Synthesis 859, 1977, 2,3-dimethylindole (4.2g) was converted to the title compound as a mixture of isomers (D1) (3.66g, 87%).

^{1}H-NMR ($CDCl_3$) 270MHz

δ	7.10-6.95	(m, 2H)
	6.75	(t, 1H)
	6.60	(d, 1H)
	3.95-3.85	(m, 0.2H)
	3.80-3.35	(m, 1.8H)
	3.32-3.15	(m, 0.2H)
	2.90-2.75	(m, 0.8H)
	1.35-1.25	(m, 4.8H)
	1.20-1.10	(m, 1.2H)

Description 2

2,3-Dihydro-2,3,3-trimethylindole (D2)



(D2)

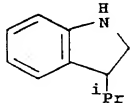
A solution of 2,3,3-trimethylindolenine (2g) in glacial acetic acid (40ml) was hydrogenated over platinum oxide (0.2g) at ambient temperature. After absorption of the theoretical amount of hydrogen (282ml), the catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was basified with saturated potassium carbonate and the product extracted into diethyl ether. The organic phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure and the residue filtered through a short silica column eluting with 40% hexane/60% diethyl ether to give the title compound (D2) (1.8g, 90%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ 7.50-6.40 (m, 4H)
3.80-3.20 (m, 2H)
1.20 (s, 6H)
1.00 (s, 3H)

Description 3

2,3-Dihydro-3-isopropylindole (D3)



(D3)

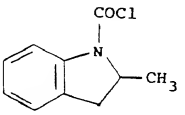
Following the procedure outlined in Description 1, 3-isopropylindole (3g) (G.F. Smith and A.E. Walters, J. Chem. Soc. 940, 1961) was converted to the title compound (D3) (1.1g, 36%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ 7.50-6.40 (m, 4H)
3.90-2.90 (m, 4H)
2.50-1.70 (m, 1H)
1.30-0.70 (m, 6H)

Description 4

1-(2,3-Dihydro-2-methyl)indolylcarbonyl chloride (D4)

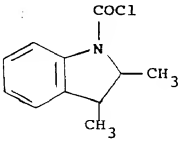


(D4)

To phosgene [13.5ml (12.5% w/w solution in toluene)] in dry dichloromethane (50ml) at 0°C was added dropwise a solution of triethylamine (2ml) and freshly distilled 2,3-dihydro-2-methylindole (2g) in dry dichloromethane (25ml). The reaction mixture was stirred at 0°C for 1h and then poured into pentane (300ml), washed with 5N sulphuric acid solution (20ml) and brine (20ml). The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (D4) (2.7g, 92%).

Description 5

1-(2,3-Dihydro-2,3-dimethyl)indolylcarbonyl chloride (D5)

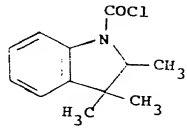


(D5)

Following the procedure outlined in Description 4, reaction of 2,3-dihydro-2,3-dimethylindole (D1) (0.5g) with phosgene [3.1ml (12.5% w/w solution in toluene)] and triethylamine (0.47ml) afforded the title compound (D5) (0.58g, 82%).

Description 6

1-(2,3-Dihydro-2,3,3-trimethyl)indolylcarbonyl chloride (D6)

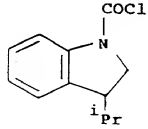


(D6)

Following the procedure outlined in Description 4, reaction of 2,3-dihydro-2,3,3-trimethylindole (D2) (0.5g) with phosgene [2.8ml (12.5% w/w solution in toluene)] and triethylamine (0.43ml) afforded the title compound (D6) (0.6g, 87%).

Description 7

1-(2,3-Dihydro-3-isopropyl)indolylcarbonyl chloride (D7)

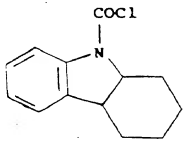


(D7)

Following the procedure outlined in Description 4 reaction of 2,3-dihydro-3-isopropylindole (D3) (1.1g) with phosgene [6.2ml (12.5% w/w solution in toluene)] and triethylamine (0.95ml) afforded the title compound (D7) (1.53g, 100%).

Description 8

1-(2,3,4,4a,9,9a-hexahydro)carbazolylcarbonyl chloride (D8)

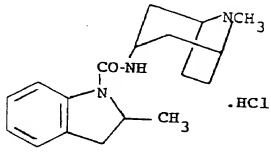


(D8)

Following the procedure outlined in Description 4, 2,3,4,4a,9,9a-hexahydro-1H-carbazole (0.7g) (G.W. Gribble and J.H. Hoffman, Synthesis 859, 1977) was converted to the title compound (D8) 0.44g.

Example 1

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2-methylindole-1-carboxamide hydrochloride (E1)



(E1)

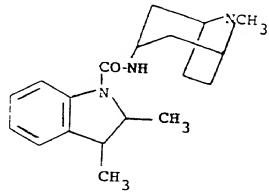
To 1-(2,3-dihydro-2-methyl)indolylcarbonyl chloride (D4) (0.5g) in dry dichloromethane (50ml) was added dropwise a mixture of (endo)-8-methyl-8-azabicyclo-[3.2.1]octan-3-amine (0.36g) and triethylamine (0.36ml) in dry dichloromethane (25ml). The reaction mixture was stirred at ambient temperature overnight, the solvent was then evaporated under reduced pressure. The residue was dissolved in 5N hydrochloric acid solution (20ml) and was washed with diethyl ether (50ml). The aqueous phase was basified with potassium carbonate and then the product was extracted into dichloromethane (3 x 50ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue filtered through a short alumina column eluting with 25% dichloromethane/ 75% chloroform. The product was isolated as the hydrochloride salt from ethyl alcohol and diethyl ether to give the title compound (E1) (0.64g, 78%) mp 292-3°C.

^{1}H-NMR (d_6-DMSO) 270MHz

δ	10.38	(bs, 1H)
	7.78	(d, 1H)
	7.18	(d, 1H)
	7.08	(t, 1H)
	6.85	(t, 1H)
	6.30	(bs, 1H)
	4.85-4.70	(m, 1H)
	3.90-3.65	(m, 3H)
	3.32	(s, 3H)
	2.85-2.00	(m, 10H)
	1.15	(d, 3H)

Example 2

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2,3-dimethylindole-1-carboxamide (E2)



(E2)

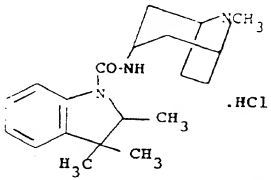
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro-2,3-dimethyl)indolylcarbonyl chloride (D5) (0.58g) with (endo)-8-methyl-8-azabicyclo[3.2.1]-octan-3-amine (0.39g) and triethylamine (0.39ml) afforded, after cystallisation from ethyl acetate, the title compound (E2) (0.43g, 35%). m.p. 134-6°C.

^{1}H-NMR ($CDCl_3$) 270MHz

δ 7.70-7.55 (m, 1H)
7.25-7.10 (m, 2H)
7.00-6.90 (m, 1H)
5.20-5.05 (m, 1H)
4.45-4.35 (m, 0.15H)
4.10 (q, 0.85H)
3.85 (dq, 0.85H)
3.65-3.50 (m, 0.15H)
3.25-3.10 (m, 2H)
2.90-2.75 (m, 1H)
2.30 (s, 3H)
2.40-2.05 (m, 4H)
1.90-1.60 (m, 4H)
1.40-1.10 (m, 6H)

Example 3

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2,3,3-trimethylindole-1-carboxamide hydrochloride (E3).



(E3)

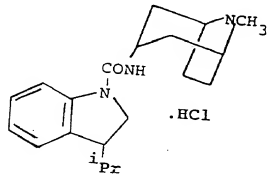
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro-2,3,3-trimethyl)indolylcarbonyl chloride (D6) (0.6g) with (endo)-8-methyl-8-azabicyclo-[3.2.1]octan-3-amine (0.38g) and triethylamine (0.37ml) afforded, after addition of ethanolic-hydrochloride, the title compound (E3) (0.5g, 51%) m.p. 225-6°C.

^{1}H-NMR (d_6-DMSO) 270MHz

δ		
	10.50	(bs, 1H)
	7.75	(d, 1H)
7.20-7.05		(m, 2H)
	6.90	(t, 1H)
	6.35	(bs, 1H)
4.45-4.30		(m, 1H)
3.90-3.70		(m, 3H)
2.90-2.05		(m, 8H)
	2.65	(bs, 3H)
	1.25	(s, 3H)
	1.15	(s, 3H)
	1.05	(d, 3H)

Example 4

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropylindole-1-carboxamide hydrochloride (E4)



(E4)

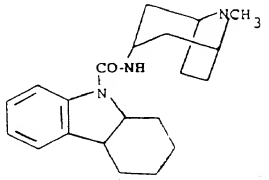
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro-3-isopropyl)indolylcarbonyl chloride (D7) (0.5g) with (endo)-8-methyl-8-azabicyclo[3,2,1]-octan-3-amine (0.31g) and triethylamine (0.31ml) afforded, after addition of ethanolic-hydrochloride, the title compound (E4) (0.7g, 86%) m.p. 278-80°C dec.

^{1}H-NMR (d_6-DMSO) 400MHz

δ	10.52	(bs, 1H)
	7.80	(d, 1H)
	7.15	(d, 1H)
	7.10	(t, 1H)
	6.85	(t, 1H)
	6.40	(bs, 1H)
	4.00-3.85	(m, 2H)
	3.85-3.65	(m, 3H)
	2.65	(s, 3H)
	2.85-1.90	(m, 10H)
	0.95	(d, 3H)
	0.70	(d, 3H)

Example 5

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3,4,4a,9,9a-hexahydrocarbazole-1-carboxamide



(E5)

Following the procedure outlined in Example 1, reaction of 1-(2,3,4,4a,9,9a-hexahydro)carbazolylcarbonyl chloride (D8) (0.44g) with (endo)-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (0.15g) and triethylamine (0.15ml) afforded, after crystallisation from ethyl acetate, the title compound (E5) (0.19g, 53%) m.p. 155-6°C.

^{1}H Nmr ($CDCl_3$) 400Mhz

δ	7.58	(d, 1H)
	7.22-7.10	(m, 2H)
	6.98	(t, 1H)
	5.12	(bd, 1H)
	4.25-4.04	(m, 2H)
	3.52-3.42	(m, 1H)
	3.28-3.16	(m, 2H)
	2.42-2.10	(m, 5H)
	2.34	(s, 3H)
	2.08-1.96	(m, 1H)
	1.96-1.50	(m, 7H)
	1.32-1.12	(m, 3H)

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

The compounds were evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats, 250-350g, were anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) was given repeatedly by the intravenous route and changes in heart rate quantified. Compounds were given intravenously and the concentration required to reduce the 5HT-evoked response to 50% of the control response (ED_{50}) was then determined.

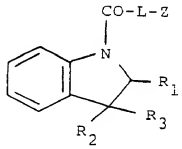
The results were as shown in Table 1.

Table 1

Compound	ID_{50} µg kg^{-1} i.v.
E1	0.79
E2	0.53
E3	1.4
E4	0.56

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

L is NH or O;

either

R_1 is methyl, R_2 is hydrogen and R_3 is hydrogen; or

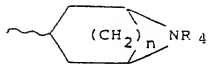
R_1 is methyl, R_2 is methyl and R_3 is hydrogen; or

R_1, R_2 and R_3 are all methyl; or

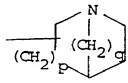
R_1 is hydrogen, R_2 is isopropyl and R_3 is hydrogen; or

R_1 is hydrogen and R_2 and R_3 together are $-(CH_2)_4-$;

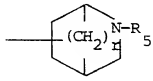
Z is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_4 or R_5 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl.

2. A compound according to claim 1 wherein L is NH.

3. A compound according to claim 1 or 2 wherein n is 2 or 3 and p, q and r are 1 or 2.

4. A compound according to any one of claims 1 to 3 wherein R_4/R_5 is methyl.

5. (endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3- dihydro-2-methylindole-1-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2,3-dimethylindole-1-carboxamide,

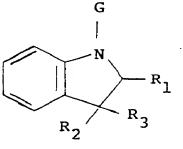
(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2,3,3-trimethylindole-1-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropylindole-1-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3,4,4a,9,9a-hexahydrocarbazole-1-carboxamide,

or a pharmaceutically acceptable salt of any of the foregoing.

6. A process for the preparation of a compound according to claim 1, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

$$J\text{-}Z^1 \qquad \text{(III)}$$

wherein
G is COQ_1, where Q_1 is a leaving group, or hydrogen; and, when G is COQ_1, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula

(II); Z^1 is Z as defined or Z wherein R_4/R_5 is replaced by a hydrogenolysable protecting group; and the remaining variables are as defined in claim 1; and thereafter optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5, and a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 5 for use as an active therapeutic substance.

9. A compound according to any one of claims 1 to 5 for use as a 5-HT_3 receptor antagonist.

10. Use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for use in the treatment of migraine, trigeminal neuralgia, visceral pain or emesis.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/00306

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 451/04, A 61 K 31/46

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
IPC[4]	C 07 D 451/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0247266 (BEECHAM GROUP PLC) 2 December 1987, see examples 4,5,6, 14,15,18; claims --	1,2,7
E	EP, A, 0287196 (BEECHAM GROUP PLC) 19 October 1988, see example 10; claims ----	1,2,7

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
3rd July 1989	26 07. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8900306 SA 27850

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 18/07/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0247266	02-12-87	AU-A- 6712187	09-07-87
		JP-A- 62252764	04-11-87
EP-A- 0287196	19-10-88	JP-A- 63222169	16-09-88

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82